

## A practical large-scale synthesis of 17 $\alpha$ -acetoxy-11 $\beta$ -(4-*N,N*-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione (CDB-2914)☆

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### Abstract

A new practical synthesis of 17 $\alpha$ -acetoxy-11 $\beta$ -(4-*N,N*-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione (CDB-2914) is described. The synthesis gives easily isolable solids at all steps and is amenable to large-scale process. © 2000 Elsevier Science Inc. All rights reserved.

**Keywords:** Steroids; Synthesis; Antiprogestins

### 1. Introduction

The 1980s witnessed the synthesis, biologic evaluation, and clinical applications of an entirely new class of steroid antagonists [1]. Spearheaded by Roussel–Uclaf, a wide variety of 11 $\beta$ -substituted analogs of 19-nortestosterone were explored as antiprogestational agents [2]. The most well-known of these compounds is mifepristone [3]. This drug has been studied extensively for both contraceptive and therapeutic applications and is marketed as an abortifacient in several European countries. Since the discovery of mifepristone (RU-38,486) as an important antiprogestational agent, there have been a vast amount of synthetic efforts aimed at producing new and improved compounds with similar pharmacological actions [4]. Cook et al. have reported the synthesis of 17 $\alpha$ -acetoxy-11 $\beta$ -(4-*N,N*-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione (CDB-2914) [5,6].

Unlike many of the compounds prepared by Roussel–Uclaf, Schering AG, and Organon [4], CDB-2914 is derived from 19-norprogesterone [5,6] and thus its pharmacological spectrum is also different. It was found that CDB-2914 is an orally more potent antiprogesterin than mifepristone in the rat. When given orally at noon on the day of proestrus, both CDB-2914 and mifepristone showed dose-dependent antiovulatory activity. However, CDB-2914 was about eight times more potent than mifepristone [7]. Hence, CDB-2914 may prove to be an effective emergency postcoital contraceptive in women [8].

For Phase I and II clinical trials [8] a large quantity (2.0 kg) of CDB-2914 was required. Although the original synthesis [5,6] was based on well known reactions, it was not suitable for large-scale processes. Several steps in the reported synthetic sequence involved the use of reagents that were especially hazardous and difficult to adapt for large-scale preparations. For example, the sequence utilizes osmium tetroxide hydroxylation, Swern oxidation, and Birch reduction. In addition, several steps required chromatographic purification of intermediates that is cumbersome and prohibitively expensive when working on a large scale. Furthermore, the number of steps and the overall yield of the process were unacceptable for the large amount of material required.

With the above considerations in mind, process development for an efficient large-scale synthesis of CDB-2914

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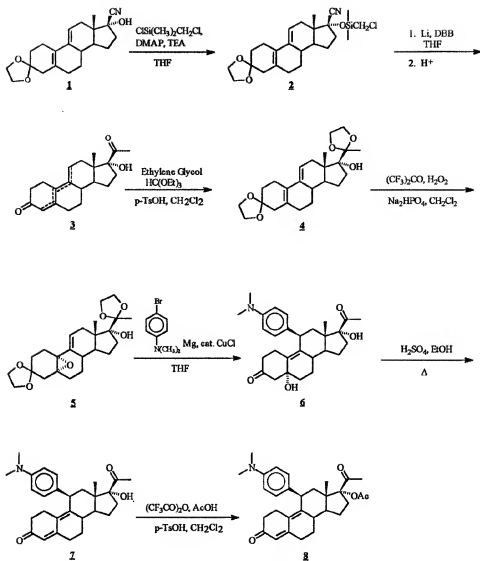


Fig. 1. Synthesis of CDB-2914.

was sought avoiding some of the problems associated with the original synthesis [5,6]. Our goal in developing this synthesis (Fig. 1) was to have fewer, high yielding steps and those steps must be amenable to bulk production of CDB-2914 with regard to time and safety factors. Furthermore, we sought to obtain synthetic intermediates that could be isolated readily by crystallization that would preclude the use of laborious chromatograms for the isolation and purification of synthetic intermediates. This work has been described in a recently awarded patent [9].

## 2. Experimental

Melting points (m.p.) were determined on a Thomas-Hoover apparatus and are uncorrected. Nuclear magnetic

resonance spectra were recorded on a Varian EM-390 (90 MHz) spectrometer as deuteriochloroform solutions using tetramethylsilane (TMS) as an internal standard ( $\delta = 0.0$ ). Infrared (IR) spectra were recorded on a Perkin-Elmer model 1600 FTIR instrument equipped with a diffuse reflectance accessory using a KBr matrix. Mass spectral analyses<sup>(EI)</sup> were conducted by Dr Susan Weintraub of the University of Texas Health Science Center at San Antonio using a Finnigan-MAT model 4615. Combustion analyses were performed by Midwest Microlabs Ltd. (Indianapolis, IN, USA).

Anhydrous/inhibitor free tetrahydrofuran (THF) was obtained from Aldrich as 18-l Kilo-Lab cylinders and was used without further purification. Solvent transfers were conducted via a cannula under an inert atmosphere. 4,4'-

Di-*tert*-butylbiphenyl (DBB) was obtained from Frinton Laboratories (Vineland, NJ, USA). 4-Bromo-*N,N*-dimethyl aniline was obtained from Janssen Chemicals. Cyanohydrin-ketal (1) was purchased from Roussel–Uclaf and assayed as follows: 97% by HPLC (Novapak  $C_{18}$ , 40% aq.  $CH_3CN$  at 1.0 ml/min,  $uv = 260$  nm), m.p. = 174–177°C,  $[\alpha]_D = 157.7^\circ$ ,  $CHCl_3$ . All other solvents and reagents were ACS reagent grade or better and were used without further purification.

Large volume additions were conducted under an inert atmosphere using a Fluid Metering, Inc. pump (Model QV) equipped with a stroke rate controller (Model QV 100). The pump was fitted with Aldrich Chem-flex tubing and 12 gauge needles. HPLC analyses were performed using a Waters and Associates system comprised of the following components: Novapak  $C_{18}$  column 3.9  $\times$  150 mm, Model 6000A pumps, Model 481 UV/Vis detector, Model 680 gradient controller, and Model 730 data module. Analytical TLC plates (silica gel GHLF, cat. # 21521) were obtained from Analtech (Newark, DE, USA).

2.1. 3-Ethylenedioxy-17 $\beta$ -cyano-17 $\alpha$ -chloromethyl-(dimethyl)silyloxyestra-5(10),9(11)-diene (2)

Under argon, cyanohydrin ketal (1) (700 g, 2.05 mol) was dissolved in THF (5 l). Dimethylamino pyridine (58 g, 0.47 mol) was added followed by the addition of freshly distilled triethylamine (335 ml, 2.4 mol). Chloro(chloromethyl)dimethylsilane (300 ml, 2.28 mol) was added dropwise and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with hexanes (5.0 l). After the mixture was stirred for 10 min, it was filtered through a pad of Celite under a blanket of argon. The solids were rinsed with additional hexanes. The filtrate was evaporated in vacuo. The material thus obtained was dissolved in ether (1500 ml) and the solution was loaded onto a pre-equilibrated column of silica gel (20  $\times$  15 cm) contained in a large flash column (15  $\times$  70 cm). The column was developed with ether and ~1800 ml fractions were collected. The first three fractions contained most of the product and were combined and evaporated in vacuo to afford 939 g (98%) of (2) as a white solid, m.p. = 80–82°C.

NMR ( $CDCl_3$ )  $\delta$  0.38 (s,  $OSi(CH_3)_2$ ), 0.91 (s, C-18 Me), 2.86 (s,  $OSi(CH_3)_2$ ), 3.99 (br.s., ketal), 5.61 (br.s., C-11 H) ppm. FTIR  $\nu_{max}$  3034, 2977, 2947, 2865, 2230 (CN), 1256 & 1235 ( $-OCH_2CH_2O-$ ), 1131 ( $-SiOCH_3$ )  $cm^{-1}$ . MS(EI):  $m/z$  (relative intensity) 448( $M^+$ , 33), 447( $M^+-H$ , 100), 419(43), 308(43), 295(40), 236(48), 99(54), 86(84). Analysis calculated for  $C_{24}H_{34}ClNO_3Si$ : C 64.33, H 7.65, N 3.13; Found: C 64.15, H 7.53, N 3.11.

2.2. 17 $\alpha$ -Hydroxy-19-norpregna-4,9-diene-3,20-dione (3)

Note: All glassware used in the following procedure was oven-dried, assembled while hot, and cooled under an argon atmosphere.

Under an argon atmosphere, 30% lithium dispersion in mineral oil (~300 g, 13.0 mol) was poured into a pressure equalizing addition funnel (2.0 l) fitted onto a 2.0 l single neck flask. The addition funnel was charged with anhydrous pentane (ca. 900 ml) and the mixture was swirled gently and left undisturbed for 45 min to allow the lithium metal to migrate to the top. The lower, oil/pentane layer was drained off and the oil/pentane solution, which contained some finely divided lithium residues, was cautiously decomposed with the addition of ethanol. The funnel was fitted to the 12-l reaction flask and the addition funnel was charged with THF (~750 ml). The slurry was drained into the 12-l reaction flask with the residual lithium rinsed into the reaction vessel with additional THF (~500 ml). The flask was fitted with a stirring shaft with a glass paddle and stirred gently. Di-*t*-butyl biphenyl (500 g, 1.88 mol), dried in vacuo for 24 h against  $P_2O_5$ , was dissolved in THF (~1300 ml), and transferred to the reaction flask containing the lithium slurry. During the addition, the mixture took on the blue/green color of the anion-radical. The mixture was stirred for 2.5 h at room temperature and then the flask was cooled in a dry ice/isopropanol bath to < -70°C. Silyl ether (2) (939 g, 2.10 mol) in THF (~2.4 l) was added using a pump at such a rate as to maintain the green color of the anion-radical (~2.25 h). When the addition was complete, dichloromethane (~400 ml) was added carefully while maintaining the temperature at ~ -70°C. When gas evolution had ceased, hydrochloric acid solution (~4 l, 6 N) was added carefully and the reaction mixture was stirred and allowed to warm to room temperature overnight. The volatiles were evaporated in vacuo. The aqueous mixture was extracted with dichloromethane (3X). The dichloromethane extract was washed with water (3 l) and brine (3 l) and dried over sodium sulfate. The solvent was evaporated in vacuo to afford a solid, which was a mixture of (3) and DBB. The solid was partitioned between 90% methanol and hexanes (3  $\times$  2500 ml each). The combined 90% methanol extracts were evaporated in vacuo, diluted with water and extracted with dichloromethane (3X). The dichloromethane extracts were washed with water and brine, combined, and dried over sodium sulfate. The solvent was evaporated in vacuo to give 595.5 g (90%) of diketones (3) as a 4/1 mixture of 4,9/5(10), 9(11) diene-3, 20-diones as determined by NMR. By TLC (5% acetone/dichloromethane), the material was sufficiently pure and was used without further purification in the following ketalization reaction. Evaporation of the hexane extract allowed for the recovery of the DBB, which was recrystallized from dichloromethane/methanol to give DBB of suitable purity for reuse in subsequent batches.

NMR ( $CDCl_3$ )  $\delta$  0.87 (s, C-18 Me), 2.30 (s, C-21 Me), 5.71 (br.s., C-4 H) ppm.

2.3. 3,20-bis-Ethylenedioxy-17 $\alpha$ -hydroxy-19-norpregna-5(10),9(11)-diene (4)

Diketone (3) (594 g, 2.10 mol) was dissolved in dichloromethane (3.8 l). Ethylene glycol (540 ml, 10.65 mol), distilled triethylorthoformate (864 ml, 5.19 mol) and *p*-toluene

sulfonic acid monohydrate (21.6 g, 0.11 mol) were added and the mixture was stirred overnight at room temperature. Saturated sodium bicarbonate solution (2150 ml) was added and stirred for 10 min. The organic layer was washed with water and brine. The aqueous washes were extracted with additional dichloromethane and the combined extract was dried over sodium sulfate. The solvent was evaporated in vacuo to afford a thick syrup. While the flask was still attached to the rotary evaporator, methanol (~3 l), containing pyridine (0.5%), was drawn into the flask to induce crystallization. After chilling the flask to 4°C, the solid was filtered and washed with methanol containing pyridine and dried in vacuo overnight to give 506.4 g (67.3%) of (4), m.p. = 170–172°C. The above material was homogenous by TLC (5% acetone/dichloromethane) and was used without further purification in the following reaction.

NMR ( $\text{CDCl}_3$ )  $\delta$  0.78 (s, C-18 Me), 1.37 (s, C-21 Me), 3.99 (m, ketals), 5.57 (br.s., C-11 H) ppm. Analysis calculated for  $\text{C}_{24}\text{H}_{34}\text{O}_5$ : C 71.61, H 8.51; Found: C 71.53, H 8.50.

**2.4. 3,20-bis-Ethylenedioxy-17 $\alpha$ -hydroxy-5 $\alpha$ ,10 $\alpha$ -epoxy-19-norpregn-9(11)-ene (5)**

Hexafluoroacetone trihydrate (266 g, 1.6 mol) was weighed into a 3 neck, 12 l round bottom flask. Dichloromethane (2500 ml) was added and the mixture was stirred vigorously at 4°C. Sodium phosphate, dibasic (125 g, 0.88 mol) was added, followed by the addition of 30% hydrogen peroxide (242 ml, 2.36 mol) and stirred for 20 min. A dichloromethane (2500 ml) solution of (4) (439.7 g, 1.23 mol) was chilled to 0°C and added to the above mixture. The mixture was stirred at 4°C for ~7.5 h. TLC analysis (25% ethyl acetate/dichloromethane) showed the reaction to be complete. Sodium sulfite (10%) solution (3 l) was added and the mixture was stirred for 30 min. The mixture was extracted with dichloromethane (3 $\times$ ), washed with water (2  $\times$  3 l) and brine (1  $\times$  2 l), dried over sodium sulfate, and concentrated in vacuo. The residue was triturated with ether and the resulting solid was filtered and washed with ether to afford 250.5 g (54.3%) of epoxide (5) m.p. = 188.5–191.5°C. NMR analysis showed none of the 5 $\beta$ ,10 $\beta$ -epoxide to be present.

NMR ( $\text{CDCl}_3$ )  $\delta$  0.79 (s, C-18 Me), 1.36 (s, C-21 Me), 3.92 (m, ketal), 6.03 (m, C-11 H of  $\alpha$ -epoxide) ppm. FTIR:  $\nu_{\text{max}}$  3510(OH), 2947, 2887, 2669, 1649, 1469, 1438, 1220  $\text{cm}^{-1}$ . MS(EI)  $m/z$  (relative intensity) 418( $\text{M}^+$ , 18), 400( $\text{M}^+ - 18$ , 77), 293(35), 141(30), 131(92), 115(56), 87(100). Analysis calculated for  $\text{C}_{24}\text{H}_{34}\text{O}_6$ : C 68.88, H 8.19; Found: C 68.70, H 8.09.

**2.5. 3,20-bis-Ethylenedioxy-5 $\alpha$ ,17 $\alpha$ -dihydroxy-11 $\beta$ -(4-N,N-dimethylaminophenyl)-19-norpregn-9-ene (6)**

Activated magnesium (72.5 g, 2.98 mol) was weighed into a dry 12-l-neck flask that was subsequently fitted with an argon inlet, reflux condenser, and a stir shaft fitted with

a Teflon paddle. Several crystals of iodine and 1.0 ml of dibromoethane were added, followed by the addition of THF (1000 ml). The mixture was stirred gently and a THF (2000 ml) solution of *p*-bromo-*N,N*-dimethylaniline (597.5 g, 2.99 mol) was added at such a rate as to maintain a gentle reflux. Upon completion of the addition, the mixture was stirred for 1.5 h and allowed to come to room temperature. Copper (I) chloride (29.5 g, 0.30 mol) was added and the mixture was stirred for 30 min at room temperature. Epoxide (5) (250 g, 0.6 mol) in THF (1500 ml) was added over ~30 min and the mixture was stirred for 1 h. Ammonium chloride solution (800 g/4500 ml water) was added and stirred for 30 min.

While stirring, air was bubbled through the solution until the mixture turned blue, indicating the complete oxidation of Cu(I) to Cu(II). The layers were separated and the organic layer was diluted with ether (4500 ml). The ether/THF layer was washed with 2.0 N ammonium chloride solution (5  $\times$  1000 ml), water, and brine. The organic extract was percolated through sodium sulfate contained in a large funnel and the filtrate evaporated in vacuo. The residue was triturated with ether (1000 ml) and the resulting solid was filtered, washed with ether, and dried in vacuo to afford 245.8 g (76%) of Grignard product (6), m.p. = 236–240°C dec.

NMR ( $\text{CDCl}_3$ )  $\delta$  0.42 (s, C-18 Me), 1.38 (s, C-21 Me), 2.9 (s,  $\text{N}(\text{CH}_3)_2$ ), 3.97 (br. m, 3,20-diketal), 4.2 (d, C-11 H), 6.65 and 7.08 (d, aromatic H) ppm. FTIR:  $\nu_{\text{max}}$  3573, 3543, 3087, 2976, 2874, 1612, 1516, 1484, 1371, 1214, 1100  $\text{cm}^{-1}$ . MS(EI)  $m/z$  (relative intensity) 539( $\text{M}^+$ , 83), 521( $\text{M}^+ - 18$ , 57), 324(21), 238(26), 87(100). Analysis calculated for  $\text{C}_{32}\text{H}_{43}\text{NO}_6$ : C 71.21, H 8.40, N 2.60; Found: C 71.29, H 8.35, N 2.74.

**2.6. 11 $\beta$ -(4-N,N-dimethylaminophenyl)-17 $\alpha$ -hydroxy-19-norpregna-4,9-diene-3,20-dione (7)**

A mixture of ethanol (4450 ml) and sulfuric acid (8.5%, 445 ml) was sparged with argon for 10 min. Grignard product (6) (244.4 g, 0.45 mol) was added as a solid with stirring and the mixture was heated to reflux for 1 h. TLC (10% acetone/dichloromethane) showed the reaction complete. The mixture was cooled in an ice bath and neutralized with saturated  $\text{NaHCO}_3$  solution. The solids were removed by filtration and washed well with ethanol and discarded. The filtrate was evaporated in vacuo, water was added, and the aqueous mixture was extracted with dichloromethane. The extract was washed with water and brine, dried over  $\text{Na}_2\text{SO}_4$ , and evaporated to a stable foam. The product was recrystallized from ether. A total of 172.5 g (88%) of (7) was obtained in three crops. m.p. 125–128°C.

NMR  $\delta$  0.47 (s, C-18 Me), 2.26 (s, C-21 Me), 2.90 (s,  $\text{N}(\text{CH}_3)_2$ ), 4.38 (d, C-11 H), 5.77 (br.s., C-4 H), 6.65, and 7.02 (d, aromatic H) ppm. FTIR:  $\nu_{\text{max}}$  3448(OH), 3074, 1709(C=O), 1643, 1602(conjugated C=O), 1560, 1519, 1440  $\text{cm}^{-1}$ . MS(EI)  $m/z$  (relative intensity): 433( $\text{M}^+$ , 35),

280(7), 134(21), 121(100). Analysis calculated for  $C_{28}H_{35}NO_3$ : C 77.56, H 8.14, N 3.23; Found: C 77.54, H 7.98, N 3.46.

**2.7. 17 $\alpha$ -Acetoxy-11 $\beta$ -(4-*N,N*-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione (8)**

Under an argon atmosphere, acetic acid (450 ml, 7.84 mol) was added to a well stirred mixture of trifluoroacetic anhydride (1100 ml, 7.84 mol) in dichloromethane (3050 ml) and the mixture was stirred at room temperature for 30 min. *p*-Toluene sulfonic acid monohydrate (67.6 g, 0.36 mol) was added and the mixture was cooled to 0°C. The 17-hydroxy product (7) (169.3 g, 0.39 mol) was dissolved in a minimum amount of dichloromethane (~400 ml), cooled in an ice bath and added to the stirred mixed anhydride. TLC (10% acetone/dichloromethane) analysis after 20 min indicated the reaction to be complete. Cold potassium carbonate solution (1200 g  $K_2CO_3$ /2 l water) was added carefully until the mixture was basic (~3600 ml). The mixture was diluted with water until the dichloromethane layer became the lower layer. The mixture was extracted with dichloromethane (3 $\times$ ) and washed with water (2 $\times$ ) and brine, dried over  $Na_2SO_4$  and evaporated to afford a thick syrup.

The syrup was dissolved in ethyl acetate (300 ml) and evaporated (2 $\times$ ). Ethanol (3.5 ml/g) was added and the mixture was heated to effect dissolution. The mixture was treated with charcoal, filtered through a pad of Celite with the Celite pad rinsed with additional ethanol. The filtrate was evaporated in vacuo and material obtained was dried in vacuo overnight. Ethanol (1 ml/g) was added and the resulting solid was broken up until homogeneous. The solid was filtered and washed with ethanol and air dried to give 123.9 g (68%) of product (8).

Final purification of (8) involved recrystallization of several combined batches from 20% aqueous ethanol at 2.5 ml/g. Processing of (8) in this manner gave material that was greater than 98% pure by HPLC (Waters Novapak  $C_{18}$ , 30% aq. MeOH with 0.033% TEA at 1.0 ml/min,  $uv = 302$  nm) and exhibited a  $m.p. = 183$ – $185^\circ C$ .

NMR ( $CDCl_3$ )  $\delta$  0.36 (s, 18- $CH_3$ ), 2.08 (s, C-17 OAc), 2.13 (s, C-21 Me), 2.90 (s,  $N(CH_3)_2$ ), 4.42 (d, C-11 $\beta$  H), 5.80 (br.s., C-4 H), 6.68 and 7.03 (d of d, aromatic H) ppm. FTIR:  $\nu_{max}$  2945, 1735, 1714, 1664, 1563, 1518, 1441, 1351, 1305, 1252, 1203, 1171  $cm^{-1}$ . MS(EI):  $m/z$  (relative intensity) 475( $M^+$ , 41), 134(18), 121(100). Analysis calculated for  $C_{30}H_{37}NO_4$ : C 75.76, H 7.84, N 2.94; Found: C 75.80, H 7.96, N 3.09.

### 3. Results and discussion

Starting from 17 $\beta$ -cyanohydrin-3-ketal (1), our strategy involved elaboration of the pregnane side chain, manipulations to allow the introduction of the 11 $\beta$ -substituent, and acetylation. 17 $\beta$ -Cyanohydrin-3-ketal (1) was purchased

from Roussel–Uclaf and is currently available domestically from Davos Chemical Corporation and Syngest, Inc.

Typically, transformation of 17 $\beta$ -cyanohydrins into the pregnane side chain has been achieved via a multi-step sequence (protection of the 3-ketone and 17-hydroxyl, addition of methyl lithium or methyl Grignard to the nitrile or aldehyde, and hydrolysis or oxidation) [10]. In 1990, Livingston et al. reported a novel one step method for the transformation of 17 $\beta$ -cyanohydrins into the pregnane side chain based on the intramolecular addition of the anion derived from the 17 $\alpha$ -(chloromethyl)dimethylsilyl ether to the 17 $\beta$ -nitrile [11]. This procedure has been given the acronym SNAP (Silicon Nucleophile Anellation Process) [10]. Accordingly, we have adapted this procedure to construct the pregnane side chain from cyanohydrin (1).

Reaction of (1) with chloro(chloromethyl)dimethylsilyl ether 17 $\alpha$ -(chloromethyl)-dimethylsilyl ether (2) in excellent yield. Addition of a THF solution of (2) to the anion radical, generated from the reaction of lithium with 4,4'-di-tert-butylbiphenyl (DBB) [12], followed by acid quenching, gave 17 $\alpha$ -hydroxy-20-keto pregnane (3) in good yield. In early large-scale efforts, we found it necessary to use a large excess (five equivalents each) of lithium wire and DBB to ensure we could properly conduct the reaction in a 'normal' working day. However, due to economic and time considerations, we sought to reduce the amount of DBB used and still obtain acceptable yields of (3).

It has been noted that because DBB is such an efficient electron transfer agent, we reasoned that it should be possible to use DBB in a catalytic fashion [13]. This would require the use of lithium powder to ensure the requisite rapid formation of the radical anion. We were able to generate (3) from (2) using 10 mol% DBB and 5 equivalents of lithium sand, but the addition of (2) was inconveniently slow. A solution was realized through the use of one equivalent of DBB and 5 equivalents of lithium sand. Under these conditions, we typically ran the reaction at near kilogram quantities of (2) to afford (3) in 90–95% yield as a solid. Furthermore, through a nonchromatographic process, we were able to conveniently recover the DBB from the reaction mixture for reuse in subsequent batches.

Conversion of diketone (3) into 3,20-diketal (4) allowed for the protection of the C-3 and C-20 ketones with concomitant migration of the 4,9-diene to the 5(10), 9(11) position. This migration places C-11 in the proper oxidation state for the introduction of the 11 $\beta$ -substituent. Thus, using a modification of the classic procedure of Teutsch et al. [14] diketal (4) was epoxidized using hexafluoroacetone/hydrogen peroxide to afford a 3:1 mixture of 5 $\alpha$ ,10 $\alpha$  and 5 $\beta$ ,10 $\beta$  epoxides. Trituration of the mixture with ether allowed for the isolation of pure 5 $\alpha$ ,10 $\alpha$ -epoxide (5) as a crystalline solid.

Reaction of epoxide (5) with the Grignard reagent derived from the reaction of 4-bromo-*N,N*-dimethyl aniline and magnesium in the presence of copper (I) chloride gave Grignard adduct (6). Once again, trituration of the crude

reaction mixture with ether gave pure (6) as a solid in 79% yield. Our ability to isolate pure 5 $\alpha$ ,10 $\alpha$ -epoxide (5) made it possible to use less of the Grignard reagent. Our procedure required the use of 5 equivalents of Grignard reagent whereas, the original procedure, using a 5 $\alpha$ ,10 $\alpha$ /5 $\beta$ ,10 $\beta$  mixture of epoxides, required 10 equivalents. In addition, after quenching the reaction with ammonium chloride solution, we found bubbling air through the mixture lead to rapid oxidation of Cu<sup>I</sup> to Cu<sup>II</sup> and ensured all of the copper salts were removed in the work up. This reduction in the amount of Grignard reagent and the complete oxidation of Cu<sup>I</sup> to Cu<sup>II</sup> gave a cleaner product that was easily isolated as a solid.

In the original procedure carried out by Cook et al. [5,6], Grignard adduct (6) was hydrolyzed to (7) and acetylated to afford (8) in a one pot reaction using phosphoric acid/acetic anhydride. However, we determined that superior yields and ease of isolation were realized by first hydrolyzing (6) to (7) with subsequent conversion of (7) to acetate (8). Thus, (6) was hydrolyzed using 8.5% sulfuric acid in ethanol to give (7) in 90% yield after recrystallization. Acetylation of (7) was carried out using the mixed anhydride formed from the reaction of trifluoroacetic anhydride and acetic acid in the presence of *p*-toluenesulfonic acid. This procedure gave acetate (8) in 70–75% yield.

Using the above described methodology, we have produced large quantities (2.5 Kg) of (8). Our methodology has noted worthy improvements over earlier, published procedures. Our synthesis contains fewer steps and can be easily scaled up without much difficulty. Furthermore, all the intermediates are isolable in suitably pure form as easily handled solids. Finally, the over all yield of our seven step synthesis, starting from (1), averages 13–15%, whereas Cook et al.'s patented nine step synthesis gave only 1.54% yield [5,6].

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